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16. ABSTRACT
Nitrogen oxides are important air pollutants which are associated with photochemical reactions in the atmosphere and adverse health effects. Although the species recently uncovered with the widely used colorimetric method invalidated much of the historical data for NO_2, relatively good measurement techniques are now available. Nitrogen oxides follow a regular diurnal pattern in urban areas reflecting both local emission sources, primarily from motor vehicles, and meteorological conditions which facilitate photochemical reactions. Although the toxicity of nitrogen oxides is not as well defined as that for other major air pollutants, evidence is accumulating that short-term exposures have different effects than the same dose administered over a longer period of time. The most important effects of NO_2 appear to be at resistance to respiratory infection, whereas atmospheric nitrates may effect respiratory allergy.

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Oxides of Nitrogen in the Atmosphere: Origin, Fate and Public Health Implications

BY JOHN H KNELSON AND ROBERT E LEE

Oxides of nitrogen, components in the formation of photochemical smog, are important air pollutants. There is accumulating evidence that short-term exposures have different health effects than long-term exposures to the same dose.

Oxides of nitrogen are important air pollutants and key components in reactions that produce photochemical smog. Although natural sources contribute a significant amount of nitrogen oxides to the atmosphere, anthropogenic sources, primarily high-temperature combustion processes, are important because they are major contributors which can be controlled. Nitric oxide (NO), a major component of photochemical smog, is present in the air at minimally hazardous concentrations which are usually less than 0.6 mg/m^3 (0.5 ppm). Indeed, even at very high concentrations, cases of human poisoning due to the gas by itself have never been reported. Only nitrogen dioxide (NO_2) and nitrates have recognized biological significance in regard to air pollution. Organic nitrogen compounds such as nitrosamines are well-recognized and important toxic materials but are mentioned only briefly in this discussion. Nearly all of the data on health implications of exposure to nitrogen oxides involve pulmonary effects, but some systemic toxicity has been suggested.

In the United States, the primary and secondary ambient air quality standard for NO_2 is 100 $\mu g/m^3$ annual arithmetic mean and 250 $\mu g/m^3$ maximum 24-hour level. However, in 1971 the US Environmental Protection Agency found that the Jacobs-Hochheiser reference method for measuring NO_2 was in error because of variable collection efficiencies and positive NO interferences (1, 2). This finding resulted in the discarding of a large amount of the previous historical data on ambient NO_2 levels and raised questions on the adequacy of the NO_2 standard.

This report reviews the atmospheric chemistry of nitrogen oxide compounds, the status of measurement techniques, ambient concentration levels, and assesses the health effects implications of these compounds.

SOURCES, ATMOSPHERIC REACTIONS, AND FATE

Of the seven oxides of nitrogen, only three are important in the atmosphere: nitrous oxide (N_2O), nitric oxide (NO), and nitrogen dioxide (NO_2). These compounds under normal conditions are gases; however, particulate forms of nitrogen compounds can also exist in the form of aerosols of nitric acid and its salts, mainly ammonium nitrate. Nitrous oxide is the most abundant oxide of nitrogen in the atmosphere with a mean concentration of about 0.45 mg/m^3 (0.25 ppm); the average annual global production of N_2O appears to be about 5.35×10^{11} kg (590×10^6 tonnes) per year (3, 4). It is generally thought that this relatively inert gas is produced mainly by bacterial action on nitrogenous compounds in the soil. Although photolysis of N_2O could produce NO, particularly above 80 kilometers, N_2O is of little importance as an air pollutant in the troposphere.

Nitric oxide and nitrogen dioxide are the most important nitrogen oxide air pollutants and are usually referred to as NO_x, *i.e.*, $NO + NO_2$. Man-made emissions of NO and NO_2 total about 4.5×10^9 kg (5×10^6 tonnes) per year on a global basis compared to natural annual emissions of 4.5×10^7 kg (5×10^8 tonnes) of NO_2 (4). Thus on a total mass basis, man-made emissions account for a small fraction of NO and NO_2 emitted into the atmosphere. Nitrogenous compounds are reduced by bacteria to NO under anaerobic conditions. The NO is then rapidly oxidized in air to NO_2. Lightning has also been implicated as a possible natural source of NO_x in the atmosphere but close examination of this possible source by Junge (5) indicates that this is a negligible contribution.

Anthropogenic sources of NO and NO_2 are combustion processes in which temperatures are high enough to oxidize atmospheric nitrogen in conjunction with the rapid quenching of the hot gases, thereby minimizing decomposition of the nitrogen oxides. Some nitrogen oxides also are produced by oxidation of nitrogen compounds contained in fossil fuels, especially coal. In general, emissions from motor vehicles account for a somewhat greater proportion of anthropogenic NO_x than stationary sources, *e.g.*, in Los

Angeles, motor vehicles account for about two-thirds and stationary sources one-third of total NO_x emissions (6). NO_2 is a product of the reaction of nitric oxide with oxygen in a two-step reaction:

$$2NO \rightleftharpoons N_2O_2$$
$$N_2O_2 + O_2 \rightleftharpoons 2NO_2$$

The formation of the dimer N_2O_2 is an exothermic reaction in which a new bond is formed. Therefore, an increase in temperature will decrease the concentration of N_2O_2, which decreases the rate of reaction and the amount of NO_2 formed.

Nitric oxide can be converted to NO_2 by other reaction mechanisms, such as a chain reaction where the oxygen atoms are simply the initiators of the chain, or a free radical chain reaction with NO as the chain carrier (7). Schematically, the NO_2 photolytic cycle has the form shown in Figure 1 (8). Ultraviolet absorption from sunlight (300 nm to 400 nm) adds enough energy to break one of the N-O bonds in the NO_2 molecule, thereby releasing an oxygen atom which reacts rapidly with atmospheric oxygen to form ozone. The rapid reaction of ozone with the NO formed in the breakup of the NO_2 molecule results in the cycling of the NO_2 in the atmosphere.

Nitrogen dioxide is a precursor of photochemical oxidants produced by the complex interaction of certain hydrocarbons and hydrocarbon oxidation products with the nitrogen dioxide photolytic cycle. This cycle, which is represented below, will produce no net NO_2 or ozone:

$$NO_2 \xrightarrow{h\nu} NO + O$$
$$O + O_2 + M \rightarrow O_3 + M$$
$$O_3 + NO \rightarrow NO_2 + O_2$$

Removal processes for nitrogen oxides are poorly understood. Atmospheric analyses for oxidized nitrogen have generally revealed the presence of oxidized species equivalent to about half the suspected emissions. Ripperton *et al* (9) obtained data which were consistent with the belief that a major sink for NO_x is reaction with ozone and ultimate conversion to nitrates which are associated with predominantly submicrometer diameter particles (10, 11). Particulate nitrates could be removed by either wet or dry deposition mechanisms depending on meteorologic conditions. However, it appears that the major removal processes are taking place at ground level. It has been proposed that NO_3, N_2O_5, HNO_2, peroxyacetyl nitrate (PAN) and particulate nitrates are taken up by such surfaces as leaves, soil and man-made materials at a greater rate than has been heretofore recognized.

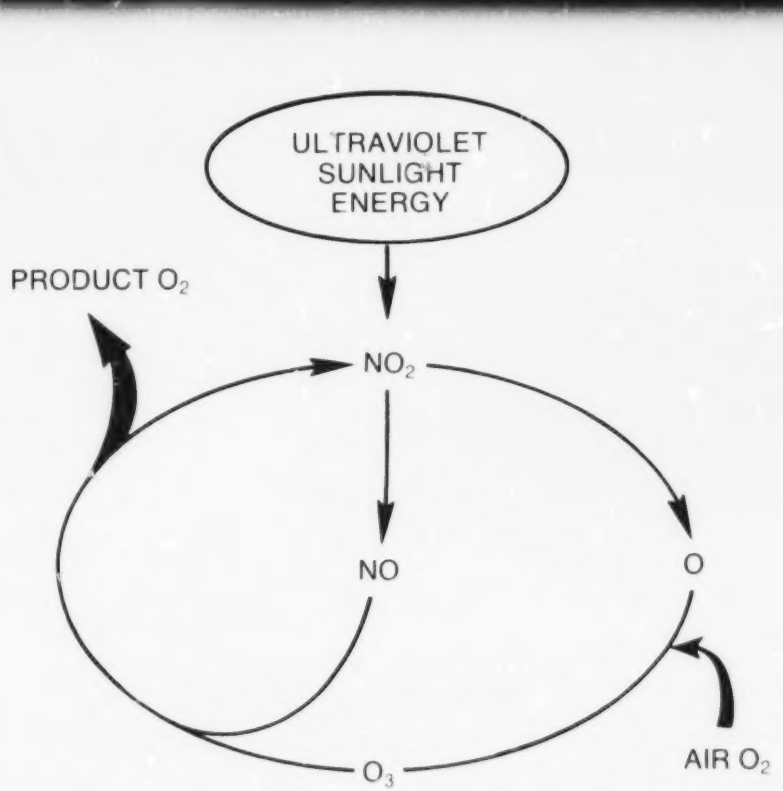

Figure 1. Atmospheric NO_2 photolytic cycle. UV absorption causes the breaking of one of the NO_2 molecules thereby releasing an oxygen atom which rapidly reacts with atmospheric oxygen to form ozone. NO_2 is recycled from the reaction of ozone and NO formed in the breakup of the NO_2 molecule.

NO_x MEASUREMENT METHODS

Manual and automated continuous methods that have been used to measure NO_x in ambient air are summarized in Table 1. The present method of choice is the chemiluminescent method which can determine both NO and total oxides of

Table 1. Summary of measurement methods for NO_x in ambient air.

Method	Type	Description	Comments	Reference
Jacobs-Hochheiser	Manual	Collection in aqueous NaOH, conversion of NO_2 to nitrite ion which is measured colorimetrically	Poor. Removal efficiency (35%), lack of constancy in correction factor dropped as EPA reference method	1, 2, 12
Sodium arsenite	Manual	Similar to Jacobs-Hochheiser method, sodium arsenite added to aqueous NaOH collection solution	Collection efficiency improved to 85%	13
Triethanolamine	Manual	Collection in aqueous solution of triethanolamine containing small amount of organic compounds, colorimetric determination of nitrite ion	Appears to be reliable	14, 15
Griess-Saltman	Manual/ automated	Diazonium salt formed from the reaction of NO_2 with sulfanilic acid is coupled with N- (1-naphthol) -ethylenediamine dihydrochloride which is measured colorimetrically	Minimal interferences	16, 17
Chemiluminescent	Automated	NO_2 quantitatively reduced to NO which reacts with ozone to produce light	Measures NO and NO_x, not subject to interferences from common air pollutants, exhibits good precision	18, 19, 20

nitrogen concurrently with dual or cyclical systems (18). Proper calibration of NO_x monitoring instruments is essential for insuring the accuracy of the measurement. Recently, nitrogen dioxide permeation tubes certified by the National Bureau of Standards (21) have been introduced for dynamic calibrations. Also, a calibration procedure based on the rapid gas phase reaction between NO and ozone to produce stoichiometric quantities of NO_2 is growing in use (22). In this procedure, the NO content of a gas cylinder containing NO in nitrogen is carefully assayed and then used to generate known concentrations of NO. This gas-phase titration procedure is versatile because with only slight modifications of the configuration it can also be used to calibrate instruments which measure NO, total oxides of nitrogen, and ozone.

AMBIENT CONCENTRATIONS OF NO_x

Atmospheric monitoring at several widely separated locations has established that NO and NO_2 can occur in the atmosphere at points considered to be remote from a polluting source. Lodge and Pate (23) observed that the average concentration of NO_2 in Panama was 1.7 $\mu g/m^3$ during the dry season and 6.8 $\mu g/m^3$ during the wet season. Ripperton *et al* (9) reported background NO_2 levels in the Piedmont area of North Carolina of 10.6 $\mu g/m^3$ at ground level and 14.3 $\mu g/m^3$ 9 m above ground level. Robinson and Robbins (24) concluded from the data presented on NO_x levels in North America that the continental average level is about 8 $\mu g/m^3$ for NO_x and about 2 $\mu g/m^3$ for NO. Their calculations indicated an average residence time of NO_2 in the air of about 3 days.

The National Air Surveillance Network (NASN) reported non-urban average levels of NO_2 as determined by the sodium arsenite procedure in the United States. In 1972 and 1973 the average NO_2 levels were below 20 $\mu g/m^3$ (25). It has been emphasized, however, that the sampling variability using the Jacobs-Hochheiser method for NO_2 analysis described previously has invalidated a major portion of the ambient air data base for NO_2. Table 2 summarizes the NO and NO_2 levels determined by the continuous Griess-Saltzman colorimetric procedure at five US cities from 1962 through 1971. The National Air Surveillaance Network method, using the arsenite procedure for 24-hour collections, has shown NO_2 levels to be well below 100 $\mu g/m^3$ on the average from 1972 through 1974 (25).

The oxides of nitrogen follow a regular diurnal pattern in urban areas, reflecting variations in emission sources and meteorological conditions as illustrated in Figure 2. Before daylight, NO and NO_2 remain relatively stable. However, as automotive traffic increases in the hours just after dawn, the concentration of the primary contaminant NO increases. As ultraviolet energy from the sun becomes available, the NO_2 concentration generally increases until nearly all of the primary NO is converted to secondary NO_2. In urban areas, the increased automobile traffic in late afternoon and evening increases concentrations of primary NO but solar energy is less available to convert NO to NO_2.

In most urban areas, NO displays a marked seasonal variation while NO_2 generally does not. For NO, as with most primary contaminants, higher mean values are observed during late fall and winter months when there is less overall atmospheric mixing and generally less ultraviolet energy available for the formation of secondary products.

N-nitroso compounds have recently been detected in air at several US sites using gas liquid chromatographic techniques. Fine, *et al* (26) reported dimethylnitrosamine levels in the ppb range in samples collected in Baltimore, Maryland and Belle, West Virginia.

Table 2. NO and NO_2 Trends at Five US Cities, 1962–1971. Average concentration, $\mu g/m^3$.*

City	NO			NO_2		
	1962-1966	1967-1971	% Change	1962-1966	1967-1971	% Change
Chicago	122.6	125.4	+ 2	86.1	101.2	+ 18
Cincinnati	43.8	53.6	+ 22	62.0	60.0	− 3
Denver	44.9	54.4	+ 21	66.0	67.9	+ 3
Philadelphia	55.2	65.4	+ 18	67.7	77.6	+ 15
St. Louis	39.8	47.6	+ 19	58.5	54.2	− 7
Average	61.2	69.3	+ 13	68.1	72.2	+ 6

*) Determined by the continuous Griess-Saltzman colorimetric procedure

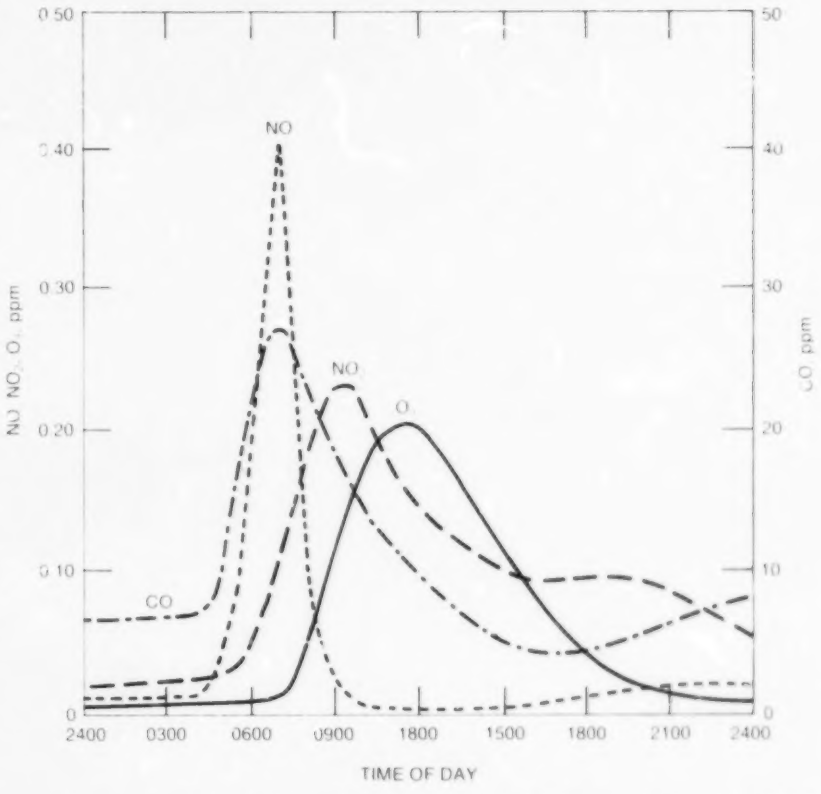

Figure 2. Diurnal variations of selected pollutants in Washington, DC, May through December, 1973 (27).

HUMAN HEALTH IMPLICATIONS OF NITROGEN OXIDES

The toxicity of nitrogen oxides is not as well defined as for other major air pollutants. In the United States the ambient air quality standard of 100 $\mu g/m^3$ as an annual arithmetic mean reflects lack of persuasive data for promulgation of a short-term standard. Evidence is accumulating, however, that short-term exposures have different effects than the same dose administered over a longer period of time.

The acute toxicity of high levels of NO_2 has been recognized in occupational exposures. Welders (27–30), silo fillers (31–33), miners (34, 35), chemists (36, 37), firemen (38), and workers in nitric acid plants (39) have encountered exposures which can produce bronchitis,

bronchiolitis, pneumonitis, pneumonia, and pulmonary edema. Short-term exposures to about 300 mg/m^3 can be fatal and short-term exposures of 50 to 200 mg/m^3 will cause the acute, severe, but reversible pulmonary effects mentioned. Five distinct clinical responses have emerged from observations of occupational and accidental exposures (40) and are summarized in Table 3.

Table 3. Known acute effects of human exposure to high concentrations of NO_2.

Concentration $\mu g/m^3$	ppm	Effect	Time between exposure and termination of effect
940 000	500	Acute pulmonary edema, fatal	Within 48 hrs
564 000	300	Bronchopneumonia, fatal	2–10 days
282 000	150	Bronchiolitis fibrosa obliterans, fatal	3–5 weeks
94 000	50	Bronchiolitis, focal pneumonitis recovery	6–8 weeks
47 000	25	Bronchitis, bronchopneumonia recovery	6–8 weeks

From reference 40

The most consistent and convincing toxicology data are from studies of effects of NO_2 on resistence to infection with pulmonary pathogens in laboratory animals. Mortality in mice challenged with a standard dose of aerosolized *Klebsiella pneumonia* following exposure to 940 $\mu g/m^3$ NO_2 during 6, 18, or 24 hours per day for 3 months was significantly greater than in animals receiving the same bacterial challenge and allowed to breath air containing no NO_2 (41, 42). Other studies have demonstrated decreased lung clearance of bacteria (43–45), depressed antibody titres (46), decreased interferon production (47, 48), and decreased bactericidal activity of lung tissue (49) from exposure to NO_2. More recently, Voisin *et al* (50) demonstrated changes in alveolar macrophage motility and bactericidal activity after NO_2 was bubbled through the aqueous culture medium. Using a similar model system, Ehrlich *et al* (51) also demonstrated an additive effect of simultaneous exposure to NO_2 and O_3 in a mouse infectivity model. There was some suggestion of synergism between the two gases upon repeated 3-hour exposure over a period of 20 days.

Gardner *et al* (52) conducted studies demonstrating a dose-rate effect of NO_2 exposure. They exposed mice to levels of NO_2 for varying periods of time prior to a standard aerosol challenge of *Streptococcus pyrogenes*. The total dose of NO_2 (i.e., concentration × time) was held constant in these experiments. Exposures to relatively high concentrations for short periods of time resulted in a greater death rate in the mice than did exposure to the same dose with lower concentrations over a longer period of time. This effect was consistent for exposure times ranging from minutes to months. These studies provide the first convincing evidence that a short-term NO_2 standard may be necessary to protect public health. Because of the marked diurnal variation of NO_2 in the atmosphere, an acceptable annual average of atmospheric NO_2 concentration may be associated with unacceptable short-term peak concentrations. Further studies are necessary to determine an appropriate short-term NO_2 standard.

Freeman and his coworkers have exposed monkeys to varying levels of NO_2 over a period of nine years (53). There is some suggestion that NO_2 exposure decreased the growth rate, and clinical signs of chronic respiratory disease have appeared in some monkeys. Examination of animals which have been sacrificed shows lung changes similar to those of emphysema and chronic obstructive lung disease seen in humans.

Von Nieding *et al* (54) found decreased diffusing capacity in humans exposed to NO_2 at 9400 $\mu g/m^3$ for 15 minutes, decreased arterial oxygen tension after exposure to 7520 $\mu g/m^3$ for 60 minutes, and increased airway resistance after 10 minutes' exposure to 3000 $\mu g/m^3$. Effects were not found at concentrations lower than those mentioned.

Whereas convincing laboratory evidence exists implicating NO_2 in decreased resistance to pulmonary infections, epidemiologic studies of human populations can only suggest such a relationship. Such studies are difficult, because human populations are usually exposed to several other air pollutants as well as to NO_2. The existence of a TNT plant in Chattanooga, Tennessee, provided an opportunity to conduct an epidemiologic assessment of NO_2 effects on respiratory disease occurrence and lung function changes in people living in various areas surrounding the source of NO_2 pollution (55, 56).

The plant operated at nearly full capacity from 1966 to 1969. Topographical and meteorological conditions resulted in prolonged exposure near the source to NO_2 concentrations typical of those measured in our largest metropolitan areas. The NO_2 exposures were determined at three schools adjacent to the source and at schools in two other more distant neighborhoods providing an exposure gradient to NO_2. The acute respiratory disease experience of second-grade elementary school children, their siblings and parents was determined at 2 week intervals for 6 months in all study areas. A total of 871 families with 4043 individuals participated. Averaged bi-weekly respiratory illness rates were statistically significantly higher for each family segment from the high NO_2 neighborhood, although rates were not consistently correlated with NO_2 exposure gradients between the three schools within the high NO_2 neighborhood. A major influenza A epidemic occurred near the onset of the health study followed by a non-influenza period and then another influenza (Type B) epidemic during the last months of the study. There was consistently more acute respiratory disease reported in the high NO_2 neighborhood during the influenza as well as the non-influenza periods. The degree of excess acute respiratory disease reported in the high NO_2 neighborhood was not as great during the epidemic as afterward, probably because of the higher base rates.

The same neighborhoods were surveyed in 1970 with regard to the frequency of more severe acute lower respiratory disease among first- and second-grade elementary school children and infants born between 1966 and 1968 (57). The incidence and frequency of bronchitis, croup and pneumonia occurring between July 1966 and June 1969 in 3217 children were determined retrospectively, and hospital records were searched to validate a sample of questionnaire responses. Bronchitis rates corresponded to the area gradient in NO_2 exposure among the larger population of school children who had lived at their current residence for 3 or more years; these area differences were statistically significant ($p < 0.01$). Among school children who had lived at their current residence for 2 years, bronchitis rates did not follw the NO_2 exposure gradient, though they were lowest in the low NO_2 neighborhood. These area differences were also statistically significant ($p < 0.02$). Among school children exposed for 1 year and among all infants, area differences in lower respiratory disease rates were not statistically significant, although the general pattern of more respiratory disease in the high NO_2 than in the low NO_2 neighborhood was maintained. Illness rates in the intermediate NO_2 area had no consistent relationship to rates among the other study groups.

Whereas NO_2 air pollution is relatively restricted to urban regions, a variety of nitrate compounds may occur in urban atmospheres and may be transported hundreds of kilometers from the source. Thus, an entirely different population at risk may exist for nitrates compared to that for NO_2.

Atmospheric nitrates may act as respiratory irritants and, if significant conversion of nitrates to airborne nitrosamine compounds should occur, the risk of carcinogenesis could exist. Charles and Menzel (58) reported that histamine is released from guinea pig lung fragments exposed to solutions of ammonium nitrate. Suspended particulate nitrates have been linked to exacerbation of asthma in a series of studies conducted by EPA in different parts of the United States (59, 60). In the New York-New Jersey metropolitan area, a study of 373 asthmatics followed daily for 8 months showed that increased asthmatic attacks were significantly associated with ambient suspended nitrates, but occurred with increased concentrations of nitrates only at temperatures of 10° centigrade or above. In another study in two southeast communities, there was evidence of excess

risk of asthmatic attacks with elevated levels of suspended nitrates at higher temperatures, but the findings were less consistent than those observed in the New York-New Jersey area.

SUMMARY AND CONCLUSIONS

Our understanding of the specific composition of the complex mixture of atmospheric nitrogen oxides and our assessment of the relative toxicity of nitrogen oxides, especially nitrates, is inadequate. As man continues to introduce many new nitrogen-containing compounds into the atmosphere, research must be conducted to qualify and quantify the nature of the pollutants themselves as well as their public health implications.

Relatively good techniques now exist for atmospheric monitoring of NO_2, but there are inadequate toxicological data for establishing good dose-response functions applicable to human health. The most important effects of NO_2 seem to be on resistance to respiratory infection. Atmospheric nitrates seem to be related to respiratory allergy, but NO_2 is not. The most urgent health research needs are in the areas of defining short-term effects of NO_2 and quantifying the effects of nitrate aerosols.

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